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Nielsen, Anne Louise; Steffensen, Kim; Larsen, Kim Lambertsen

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Cyclodextrin based polymeric particles with controlled disruption properties

Anne L. Nielsen[1], Kim Steffensen[2], and Kim L. Larsen[1]

[1]Section of Chemistry, Department of Biotechnology and Environmental Engineering, Aalborg University, Sohngaardsholmsvej 57, DK-9000 Aalborg; [2]Cheminova A/S, Thyborønvej 78, DK-7673
aln@bio.aau.dk

ABSTRACT SUMMARY

Here we present the formation of particles with controlled disruption abilities for controlled drug delivery purposes. They are made by self-assembly of cyclodextrin (CD) polymers and hydrophobically modified dextran. This is followed by a controlled disruption of the particles by addition of a trigger molecule competing for the CD cavities.

INTRODUCTION

The targeted delivery of drugs to a specific place or tissue in the human body offers numerous challenges for scientists today. Controlled delivery of powerful drugs such as chemotherapeutic agents affecting only the target tissue, leaving the healthy tissue untreated is of great interest. Several approaches have been addressed for this purpose, such as enviro-sensitive particles in the form of hydrogels [1] or encapsulation of the drug in phospholipids [2]. Particles capable of responding to external stimuli can offer the advantage of the drug being released exactly where and when it is needed.

Cyclodextrins (CD) have the ability to form inclusion complexes with a wide range of molecules. In this study polymers with CDs as pendants were made from CD derivatives and were highly water-soluble. A complementary polymer strand was made of hydrophobic modified dextrans, carrying benzoate moieties. Thereby both of the two polymer types in the formed particles are biocompatible.

EXPERIMENTAL METHODS

PVP-co-β-CD-NMA (pCD) was synthesized by free-radical polymerization from reactive CD-n-methylolacrylamide (CD-NMA) and vinylpyrrolidone (VP) in aqueous solution using azobisisobutyronitrile (AIBN) as initiator. Modified dextran was produced by a transesterification between dextran (40 kDa) and vinyl benzoate (VB) to yield dextran-benzoate (dex-BZ). Particles were formed by self-assembly from aqueous solutions of the two polymers. Solutions of each polymer were prepared and mixed in different ratios and concentration ranges. At mixing a turbid, white suspension of nano-particles was immediately observed. Measurements by dynamic light scattering (DLS) were performed within minutes of the mixing. Samples for scanning electron microscopy (SEM) were also withdrawn right after mixing and were dried on a SEM-target.

ITC measurements were carried out on a VP-ITC micro calorimeter. Titrations were performed with a 10 mM CD or a pCD solution of 10 mM CD equivalents into solutions of 1 mM of VB or dex-BZ (of approximately 1 mM BZ equivalents) in miliQ water. After thermal equilibrium of the titration cell had been reached, an initial delay of 180 seconds followed by an initial injection of titrant of 1µL was applied. After this injection, volumes from 10 to 20 µL and delay times between injections of minimum 250 seconds were applied.

RESULTS AND DISCUSSION

Hydrogel-particles were produced by simply mixing of the polymers leading to self-assembly as sketched in figure 1.

This process was studied by ITC and the complexation between the two polymer types shown to be strong compared to free monomers or polymer-monomer interaction, respectively.

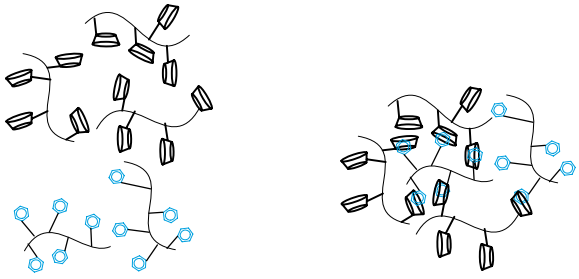

Figure 1. Sketch of self-assembly behavior.

The produced particles were in the micro-/nanometer range according to DLS and SEM studies (figure 2).

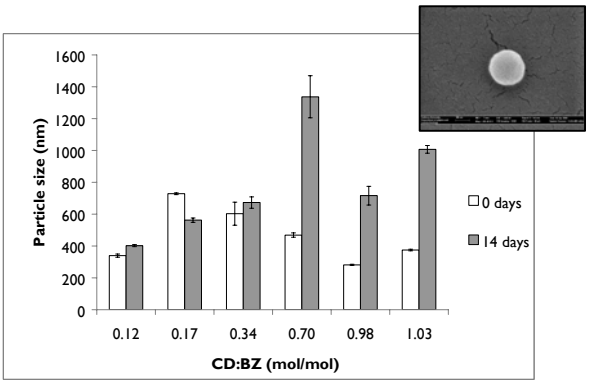

Figure 2. DLS and SEM of the produced particles. White bars show size of freshly made particles and grey bars sizes after two weeks of storage. Insert shows SEM image of one particle.

SEM analyses revealed a smaller particle size than obtained by DLS, most likely owing to the drying of particles before the analysis. The size was also found to depend on the ratio between CDs and BZs. The storage stability of the particles was assessed by DLS measurements at different time intervals (0 and 14 days in figure 2), revealing dependence between CD-BZ ratio and particle stability. This is thought to be related to a bridging between the particles over time when uncomplexed CDs are present.

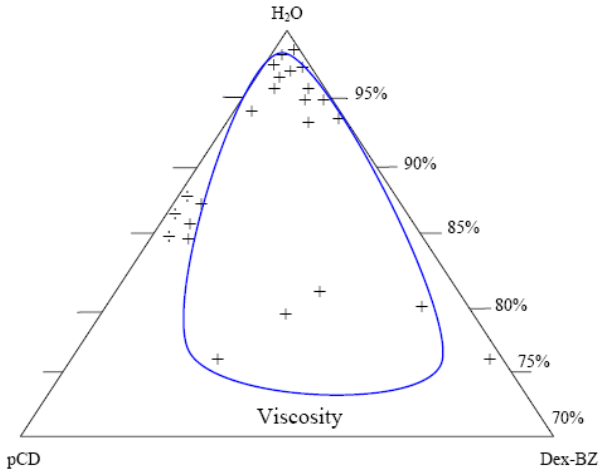

Figure 3. Phasediagram of particle formation, the blue line represents the regime where particles are formed.

Particle formation could be accomplishedis a wide variety of concentrations and ratios of the two polymers (figure 3).

Addition of adamantol to disrupt the particles by competing for CD cavities was followed by DLS measurements as shown in figure 4. This showed how the particles were able to disrupt in a controlled manner due to the addition of a molecule competing for CD cavities.

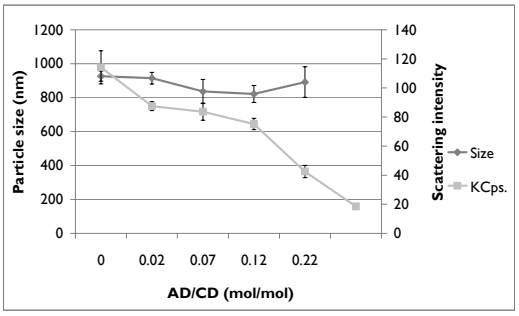

Figure 4. DLS measurements at different concentrations of adamantol added.

SEM analyses revealed that the particles lost their spherical shape upon addition of adamantol and tended to form larger aggregates.

CONCLUSION

Particles of cyclodextrin polymers and modified dextran were made by self-assembly in aqueous solution and were found to be spherical and in the nano-/micrometer range. The storage stability of the particles was found to depend on the ratio between CDs and hydrophobic pendants. Particle disruption could be achieved by addition of a trigger molecule such as adamantol competing with BZ for the CD cavities. These particles may have a future within controlled drug delivery due to their unique ability to disrupt in a controlled manner.

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